

### **REMARKS**

Claims 1, 3-5, 19, 21-34, and 37-40, 42 and 43 are pending in the present application. Among them, claims 3, 28, and 29 were previously withdrawn from further consideration, but the Examiner has indicated in the Office Action of January 20, 2011 that the subject matter of these claims will be examined. Accordingly, Applicants have changed the status identifiers of claims 28 and 29 to “Previously Presented.”

Applicants have canceled claims 3 and 42 without prejudice and amended claim 1 to clarify the subject matter claimed and incorporate elements of newly-rejoined claim 3. Support for the amendment to claim 1 can be found, for example, in claim 3 as originally filed, in paragraph [0042], and in Examples 2 and 3. No new matter has been entered.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

### ***Objection***

The Examiner has objected to claims 1 and 42 for reciting “posttranslation” rather than “posttranslational.” Applicants have amended claim 1 to remove the term, and canceled claim 42. These amendments are believed to obviate the objection.

### ***Claim Rejections under 35 U.S.C. § 112, 2nd paragraph***

Claims 1, 3-5, 19, 21-24, 37-40, 42, and 43 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Allegedly, the use of the phrase “one amino acid substitution” is unclear. Applicants respectfully traverse. Applicants have amended claim 1 and all claims depending therefrom, and canceled claim 42. The pending claims no longer recite the phrase “one amino acid substitution.” These amendments are made solely to expedite prosecution and are not made in acquiescence to the Examiner’s rejections, and

Applicants reserve the right to pursue claims of similar or differing scope in future applications. The current amendments are believed to obviate the rejections, and Applicants respectfully request reconsideration and withdrawal of the rejections.

***Claim Rejections under 35 U.S.C. § 112, 1st paragraph***

Claims 1, 3-5, 19, 21-24, 37-40, 42, and 43 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner asserts that the claimed subject matter was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Allegedly, the specification does not teach post-translational modification of a protease cleavage site of any protein, and thus, the specification lacks description of representative species encompassed by the genus of the claim. Applicants respectfully traverse. Claim 1, and all claims depending therefrom, have been amended and no longer recite the elements of post-translational modification. Claim 42 has been canceled. The amendments are made solely to expedite prosecution, and are not made in acquiescence to the Examiner's rejections. Applicants reserve the right to pursue claims of similar or differing scope in future applications. In view of the current amendments, Applicants respectfully request reconsideration and withdrawal of the rejections.

Claims 1, 3-5, 19, 21-24, 37-40, 42, and 43 are rejected under 35 U.S.C. § 112, first paragraph, because the Examiner asserts that the specification does not reasonably provide enablement for "any adzyme...wherein the adzyme comprises any post translational modification to inhibit autoproteolysis..." (page 5 of the Office Action). Allegedly, the pending claims are so broad as to encompass any adzyme comprising a protease conjugated to any targeting domain from any source having any structure, wherein said adzyme comprises a post translational modification. In addition, the specification allegedly does not provide sufficient guidance, and thus, determination of adzyme activity having the desired biological characteristics is unpredictable and would require undue experimentation.

Applicants respectfully traverse to the extent the rejection is maintained over the amended claims. Claims 3 and 42 have been canceled. Claim 1 and all claims depending

therefrom have been amended, and the claims no longer specify that the adzyme comprises at least one amino acid substitution or posttranslation modification to inhibit auto-cleavage by said protease domain. The pending claims now specify that the protease domain comprises a zymogen. The specification provides ample guidance which would enable one of skill to make and use the invention. For example, Applicants have provided working examples in which the protease domain comprises a zymogen, such as prethrombin (Examples 2), or trypsinogen and other candidate proteases that are commercially available and expressible as zymogens (paragraphs [0579] and [0600] of Example 3). Thus, in view of the amendments, reconsideration and withdrawal of the rejections are respectfully requested.

***Claim Rejections under 35 U.S.C. § 103(a)***

Applicants note with appreciation that the previous rejection of claims 1, 3-4, 21-27, 30-34, and 37 under 35 U.S.C. § 103(a) have been withdrawn after the previous amendment of claim 1. However, the Examiner raised a different 103(a) rejection, as discussed below.

Claims 1, 3-5, 21-34, 37, and 42-43 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combined teachings of Davis et al. (WO 00/64485, hereinafter "Davis") in view of Chamow et al. (Trend Biotech, 1996, 14. pp. 52-60, hereinafter "Chamow"), and Sallberg (U.S. Patent No. 6,960,569, hereinafter "Sallberg.") The Examiner asserts that no patentable weight has been given to the term "amino acid substitution," but even if the term had been considered, it would allegedly have been obvious in view of the cited references. Allegedly, Davis teaches fusion proteins that have greater catalytic activity than the unconjugated molecule and Sallberg teaches mutation of protease cleavage sites to make proteins resistant to protease cleavage. Chamow teaches bispecific immunoadhesins (immunoglobulin fusion protein) comprising two different proteins having different functions each conjugated to a constant region of an immunoglobulin. According to the Examiner, one of skill in the art would have been motivated to make the claimed invention based on the teachings of these references. Applicants traverse.

MPEP §§ 2142-2143 set out criteria for establishing a *prima facie* case of obviousness for combining prior art reference teachings to arrive at the claimed invention. To render the claimed invention obvious, the combined teachings of the cited references must teach each and every element of the claims. Further, one of skill in the art must have a motivation to combine the cited references in an attempt to arrive at the claimed invention, as well as a reasonable expectation of successfully doing so. Applicants contend that these criteria are not met. For reasons of record, the Examiner's proposed combination of Davis and Chamow fails to establish a *prima facie* case of obviousness with regard to the previously pending claims.

Nevertheless, solely to expedite prosecution, Applicants have canceled claim 42 and amended the remaining claims to more particularly point out certain embodiments of the claimed adzymes. Applicants' amendment is not in acquiescence to the rejection or any of the arguments advanced by the Examiner. Applicants expressly reserve the right to prosecute claims of similar or differing scope and to present additional arguments or evidence to address the Examiner's rejections to the previously pending claims. Applicants' amendment is believed to obviate the rejection, as described briefly below. For example, the combined teachings of Davis and Chamow fail to teach or suggest *adzymes comprising a protease domain, wherein the protease domain comprises a zymogen*. At best, Davis suggests that a zymogen is one of a number of possible types of "targeting moieties," but Davis not teach or suggest that a zymogen may be used as an element of a protease domain. In contrast, Applicants have provided a detailed description and working examples in which the protease domain of an adzyme comprises a zymogen.

Because this feature of the claimed invention is neither taught nor suggested by Davis or Chamow, the cited references fail to satisfy the criteria necessary to render the claimed invention obvious. Not only does the combination of Davis and Chamow lack all the limitations of the claims, but Applicants submit that one of skill lacks motivation to combine the references. Applicants maintain the arguments of record on this point.

Sallberg fails to remedy the deficiencies of Davis and Chamow. Sallberg discloses peptides of a Hepatitis C Virus (HCV), which may be truncated or mutated to remove a

proteolytic cleavage site in order to increase immunogenicity of the peptide. Sallberg also mentions that fusion proteins can be made from the HCV peptides in order to further increase immunogenicity. However, Sallberg does not disclose a protease domain that catalyzes the proteolytic cleavage of at least one peptide bond of the substrate polypeptide so as to inhibit the activity of the polypeptide, nor does Sallberg disclose a protease domain comprising a zymogen. Thus, Sallberg fails to disclose claim elements missing from Davis and Chamow. In addition, Sallberg does not provide any teaching or motivation to combine the HCV peptides with techniques disclosed in Davis or Chamow and therefore fails to describe any motivation to combine the references.

The Examiner appears to have hand-picked elements of the claims from a variety of sources in the literature in order to arrive at the present claims. However, in doing so, the Examiner has failed to provide a motivation for selecting the particular combination of elements set forth in the claims. Instead, it appears that the Examiner has started from the claimed invention and then identified prior art references that recite similar words or share certain categories of features. This is insufficient to undermine the patentability of the claimed invention. Moreover, this approach represents impermissible hindsight. MPEP 2142.

Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.

Applicants assert that the Examiner has not established a *prima facie* case of obviousness. There is no motivation to combine the fundamentally distinct teachings of Davis and Chamow to arrive at the claimed invention. Moreover, the cited references fail to teach or suggest each and every limitation of the claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim 5 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow and Sallberg as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Dolinar et al. (*Food tecnol and biotech.* 2000, 38, 5-9, hereinafter "Dolinar"). The Examiner asserts that Dolinar, which relates to the reversible protease inhibitor MMTS (methyl methane-thiosulfate) and refolding of a cysteine proteinase type protein, would be combined with the other references to arrive at a fusion protein complex comprising a protease using a protease inhibitor so that said fusion protein complex would not be cleaved by the protease. Applicants traverse.

As discussed above, the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach each and every element of the claims. The teachings of Dolinar do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom (e.g., claim 5) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

Claims 38-40 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davis in view of Chamow and Sallberg as applied to claims 1, 4, 19-27, 30-34 and 37 above, and further in view of Sanderson et al. (*Medic. Res. Rev.* 1999, 19, 179-197, hereinafter "Sanderson"). The Examiner asserts that Sanderson teaches a small molecule non-covalent binding protease inhibitor used in a pharmaceutical composition which is reversible and safe to humans. Allegedly, one of skill would be motivated to add such a protease inhibitor to a pharmaceutical composition comprising "an adzyme of Davis et al. and Chamow et al...as taught by Sanderson et al. to extend the shelf life of the adzyme." Applicants traverse.

As discussed above, the cited references fail to undermine the patentability of the claimed invention for, at least, failing to teach each and every element of the claims. The teachings of Sanderson do not overcome these deficiencies. If an independent claim, for example independent claim 1, is nonobvious under 35 U.S.C. § 103, then any claim depending therefrom

(e.g., claim 38-40) is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Accordingly, reconsideration and withdrawal of this rejection are requested.

### ***Double Patenting Rejection***

Applicants note that the provisional double patenting rejection over co-pending application 10/792,498 has been maintained. As acknowledged by the Examiner and pursuant to MPEP 804, “[i]f the ‘provisional’ double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the ‘provisional’ double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.”

Applicants note that no claim has, as yet, been allowed in this or co-pending application Nos. 10/792,498. Applicants will consider amendments to the claims or a terminal disclaimer, if necessary, upon indication of allowable subject matter.

### ***Co-Pending Applications***

The following co-pending, commonly assigned applications are brought to the Examiner's attention: application serial number 10/792,498 and 10/650,592. The Examiner is obviously aware of the existence of these applications as they are used in the above outlined double patenting rejection. The Examiner is invited to consider all past, present, and future prosecution in these co-pending applications.

**CONCLUSION**

Applicants submit that the application is in condition for allowance.

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. The Director is hereby authorized to charge any other deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, from which the undersigned is authorized to draw under Order No. **COTH-P02-001**.

Dated: May 26, 2011

Respectfully submitted,

By /Melissa S. Rones/  
Melissa S. Rones, J.D., Ph.D.  
Registration No.: 54,408  
ROPES & GRAY LLP  
Prudential Tower  
800 Boylston Street  
Boston, Massachusetts 02199  
(617) 951-7000  
(617) 235-9492 (Fax)  
Attorneys/Agents For Applicant